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(54) Title: SYNTHESIS OF RESVERATROL

(57) Abstract: The invention relates to novel methods of producing resveratrol. Resorecylic acid is reacted with benzyl bromide in acetone under basic conditions to give a protected benzyl ester. Treatment with KOH allows for removal of the potassium benzoate from the benzyl alcohol by-product. Acidification followed by LAH reduction gives a benzyl alcohol in high overall yield. The benzyl alcohol is converted to a bromide using phosphorus tribromide. An Arbuzov reaction is then conducted using isopropyl phosphite to give the corresponding phosphonate in high yield. Coupling with 4-benzyloxybenzaldehyde at 1:1 stoichiometry with sodium methoxide gave the E-stilbene as a single isomer in good yield. An alternative method involves a palladium catalysis. 3,5-substituted benzoic acid chlorides react with acetoxy styrene using catalytic amounts of palladium acetate and trialkylamine to give stilbene products.

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SYNTHESIS OF RESVERATROL

1. RELATED APPLICATIONS

5 This application is related to and claims the benefit of United States Provisional Application Serial No. 60/182,913 of Merritt B. Andrus, filed February 16, 2000 and entitled "Synthesis of Resveratrol, a Potent New Disease Preventative Agent" which is incorporated herein by this reference.

2. FIELD OF THE INVENTION

10 The present invention relates to methods of chemical synthesis of naturally occurring organic compounds. More specifically, the invention relates to the chemical synthesis of (E)-3,5,4'-trihydroxystilbene, hereinafter resveratrol.

3. TECHNICAL BACKGROUND

15 Plants have been a source for many of the drugs and other chemicals that humans use to fight disease and alleviate the symptoms of disease. Some plants such as herbs have been shown to contain compounds that relieve pain. Other plants have been shown to contain compounds that might be used to treat mental illness. Yet other plants contain compounds that treat are useful in treating high blood pressure. For example,
20 epicatechins, found in green tea, have been shown to prevent certain types of cancer, lower blood pressure, and reduce inflammation. Genistein, from soy beans has also been shown to prevent cancer, lower blood pressure, and reduce osteoporosis. Gordon, M. H., *Nat. Prod. Reports*, 1996, 265-287.

25 Recently, investigators have been looking for plants that contain compounds that can be used to treat cancer. For example, researchers have been looking for natural compounds that can prevent the formation and promotion of tumors. Of particular interest are agents that show the ability to fight cancer without the side effects of the currently available cytotoxic agents. One compound that shows potential to treat cancer without the harsh side effects is the simple trihydroxystilbene, resveratrol. Cai, L. et al.,
30 *Sci.* 1997, **275**: 218-221.

Resveratrol has been noted for its disease preventative qualities in humans and has been attributed as the reason for the so-called "French Paradox." The French Paradox is that although the Mediterranean diet containing high levels of fat and alcohol, the

expected increase in rates of cancer and heart disease is not observed. Renaud, S & DeLorgeril, M., *Lancet* 1992, **339**:1523.

Resveratrol is a small organic molecule naturally occurring in grape skins, mulberries, peanuts, and other plants. Resveratrol inhibits the initiation, promotion, and the progression of cancer. One group of researchers demonstrated the potent effects of resveratrol in various cellular and animal assays. *See Cai, supra*. For example, resveratrol was shown to inhibit preneoplastic lesions in mouse mammary glands induced with 7,12-dimethylbenzo(a)anthracene. Other tumor models were also used, including skin tumors and leukemia, with resveratrol showing strong inhibitory effects.

Resveratrol has been shown to have potential as a therapeutic for a range of diseases. For example, resveratrol has been shown to be a vasorelaxant, inhibiting the contractile response of the aorta to noradrenaline. Chen, C.K. & Pace-Asciak, C.R. *Gen. Pharmac.* 1996, **27**: 363-366. Others have shown that resveratrol inhibits platelet aggregation and coagulation. Goldberg, et al., *Clin. Chim. Acta* 1995, **237**: 155; Pace-Asciak, C.R. *Clin Chim Acta* 1995, **235**: 207; Arrichi H., *Chem. Pharm. Bull.* 1982, **30**: 1766.

Furthermore, many commercial uses have been conceived and patented. For example one patent was issued for use of resveratrol as an antimicrobial and fungicidal agent. Other patents have issued for using resveratrol to treat stenosis or artery stricture after surgery. Yet others have patented the use of resveratrol in cosmetics and cleansers.

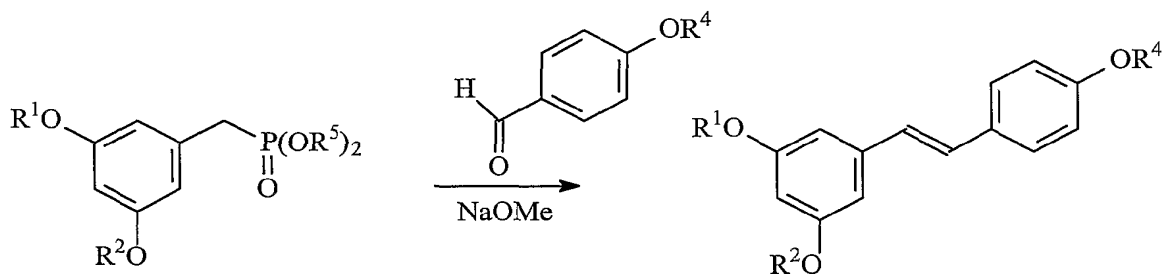
Despite the wide variety of uses for resveratrol, there is not an inexpensive source for it. Because resveratrol is present in grapes and other naturally occurring sources only in trace amounts, a large amount of grapes or other plant product must be used to isolate and purify even a limited quantity of resveratrol. A few methods of chemically synthesizing resveratrol have been introduced, although these methods require expensive starting materials which also raise the cost of producing resveratrol. The methods of synthesizing resveratrol also produce large amounts of by-products. These by-products must be removed between the various steps of the synthesis to prevent interference and contamination of the end-product. Generally, the purification of the reaction products is done by silica gel chromatography. However, such chromatography increases the overall time required for synthesis and can significantly add to the cost. Because of the product

lost during the purification and to the by-products, the overall yield of resveratrol is reduced.

In light of the foregoing, it would be an advancement in the art to provide a method of synthesizing resveratrol. It would be a further advancement if the method used inexpensive starting materials. It would be a further advancement if the method produced a high level of the desired product with limited by-products. It would be an additional advancement if the method did not require silica gel chromatography to purify the reaction products. It would be a further advancement if the method were readily scalable to mass production of resveratrol. Such methods are described and claimed herein.

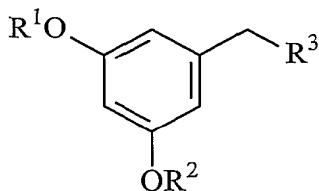
4. BRIEF SUMMARY OF THE INVENTION

The present invention relates to a method of synthesizing (E)-3,5,4'-trihydroxystilbene, resveratrol. In one embodiment a reliable Horner-Emmons coupling reaction is used to couple a benzylic phosphonate to a protected aldehyde. This route of synthesizing resveratrol is relatively inexpensive and uses readily available starting materials and reagents. The coupling step is illustrated by the following diagram:



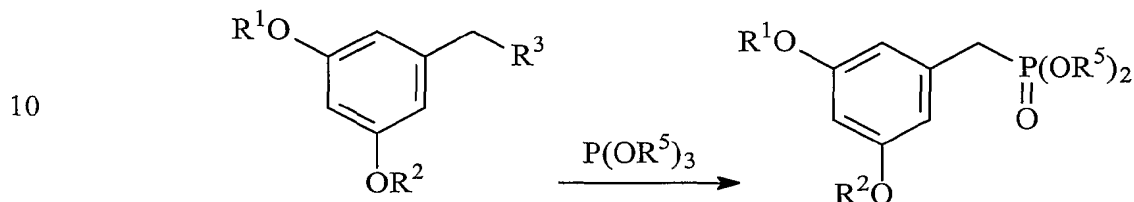
wherein R^1 , R^2 , and R^4 are protecting groups such as methyl, benzyl, alkyl, silyl, and the like. R^1 , R^2 , and R^4 can be the same protecting group or may be different protecting groups. R^5 is an alkyl group such as isopropyl, methyl, ethyl, butyl, and the like. After the coupling step the protecting groups are removed to form resveratrol.

The method of synthesizing resveratrol can begin with a starting material such as resorcylic acid. In a first step, protecting groups are added to the 3 and 5 hydroxy groups of the resorcylic acid. The 3 and 5 protecting groups can be methyl, benzyl, alkyl, and the like. Both of the protecting groups can be identical, or each protecting group can be different. Next, the carboxylic group is reduced. The reduced carboxylic group is halogenated with, for example, bromine to form a compound of the formula:



5

wherein R¹ and R² are protecting groups and R³ is a halogen. This compound is reacted with R⁴, an alkyl phosphite according to the following formula:



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R⁵ may be an alkyl group such as isopropyl, methyl, ethyl, butyl and the like. The phosphonate of this reaction can be coupled to the substituted benzaldehyde as discussed above.

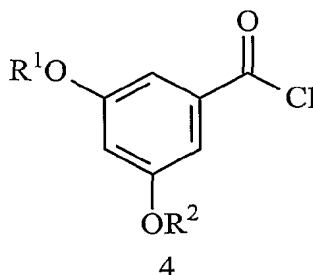
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According to one presently preferred method of synthesizing resveratrol, 3,5-dihydroxybenzoic acid is obtained as a starting material. The 3 and 5 hydroxy groups are benzylated to form 3,5-dibenzyloxybenzoic acid. Next, the carboxylic group of the 3,5-dibenzyloxybenzoic acid is reduced to form 3,5-dibenzyloxybenzyl alcohol. The hydroxy group of the reduced carboxylic acid is brominated to produce 3,5-dibenzyloxybenzyl bromide. Isopropyl 3,5-dibenzyloxybenzyl phosphonate is created by reacting the 3,5-dibenzyloxybenzyl bromide with triisopropyl phosphite. The phosphonate is coupled with 4-benzyloxybenzaldehyde to form (E)-3,5,4'-tribenzyloxystilbene via a Horner-Emmons coupling reaction. Finally, the 3, 4', and 5 benzyl groups are removed to form resveratrol.

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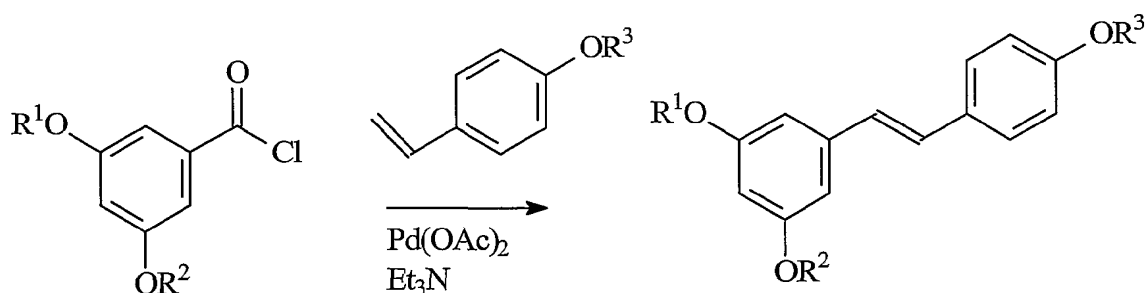
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The present invention also relates to another method of synthesizing resveratrol involving a palladium catalyst. Generally, the method involves obtaining a compound of the following formula:



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wherein R^1 and R^2 are protecting groups such as methyl, alkyl, and benzyl. The compound is coupled with a protected 4-hydroxystyrene via a Heck coupling as follows:



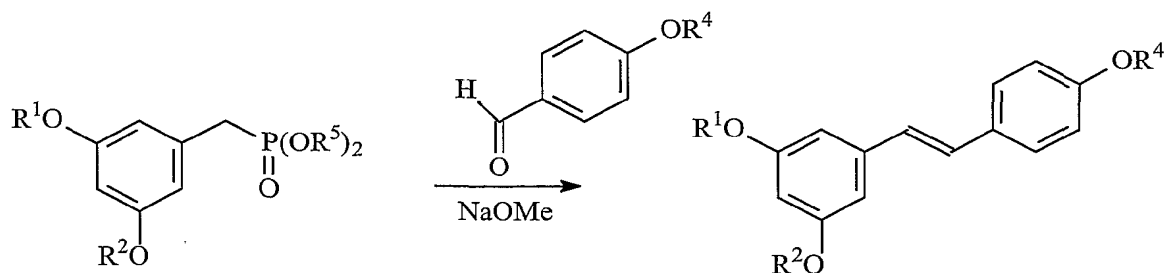
to yield a protected 3,5,4'-trihydroxystilbene. R^3 can be a protecting group such as methyl, alkyl, and benzyl as well as an aceto group. When R^3 is an aceto group, the protected 4-acetoxy-3',5'-hydroxystilbene can be converted to a protected (E)-3,5-dihydroxy-4'-hydroxystilbene by removing the aceto group under basic conditions. Next, the 3 and 5 protecting groups are removed to yield resveratrol. In other embodiments where R^3 is a protecting group such as methyl, alkyl, or benzyl, all three protecting groups may be removed in the same step.

In a presently preferred embodiment of the invention, resveratrol is made according to the following method. A quantity of 3,5-dimethoxybenzoyl chloride is coupled with 4-acetoxystyrene to form (E)-4-acetoxy-3',5'-dimethoxystilbene. A Heck reaction using a palladium catalyst is used for the coupling step. A base is added to the (E)-4-acetoxy-3',5'-dimethoxystilbene to remove the 4-aceto group and form (E)-3,5-dimethoxy-4'-hydroxystilbene. The methyl groups can be removed by the addition of BBr_3 to yield resveratrol.

These and other advantages of the present invention will become apparent upon reading the following detailed description and appended claims.

5. DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to direct, efficient methods of synthesizing resveratrol from readily available inexpensive starting materials. In one presently preferred embodiment, resveratrol is synthesized with a key Horner-Emmons coupling step. A phosphonate is coupled to a protected para-hydroxybenzaldehyde in the presence according to the following reaction:



wherein R^1 , R^2 , and R^4 , are protecting groups, and R^5 is an alkyl group such as methyl, ethyl, isopropyl, butyl, and the like. The protecting groups can be benzyl groups, methyl groups, alkyl groups, or the like. The yield of this reaction step is in the range of about 72%.

5 The protecting groups may be the same for R^1 , R^2 , and R^4 . For example, in one embodiment, each of the protecting groups is a benzyl group. Thus, 3,5-dibenzyloxybenzyl phosphonate is coupled to 4-benzyloxybenzaldehyde. (E)-3,5,4'-tribenzyloxystilbene is formed from the coupling step in about an yield. After the coupling step, the protecting groups are removed, resulting in resveratrol with about 80% efficiency.

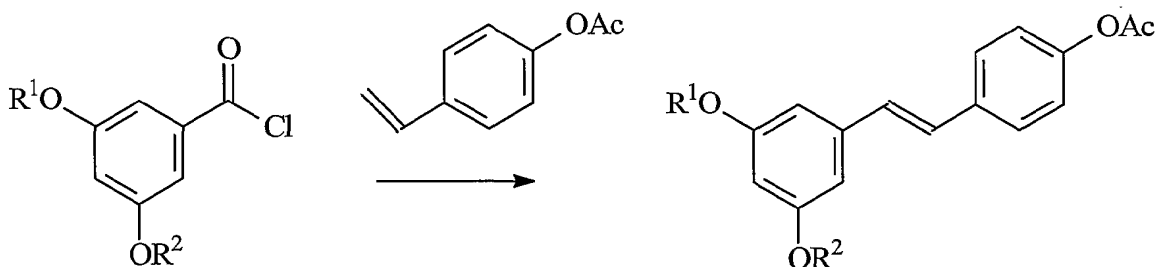
10 There are many potential routes for producing the protected benzyl phosphonate of the above reaction. In one such reaction, 3,5-dihydroxybenzoic acid is the starting material. A protecting group is added to each of the 3 and 5 hydroxy groups. For example, benzyl bromide can be reacted with the 3,5-dihydroxybenzoic acid to give 3,5-dibenzyloxybenzoic acid. Next, the carboxylic group of the benzoic acid is reduced to produce the corresponding alcohol. For example, LAH is reacted with the 3,5-dibenzyloxybenzoic acid to give 3,5-dibenzyloxybenzyl alcohol. The overall yield of 3,5-dibenzyloxybenzyl alcohol from 3,5-dihydroxybenzoic acid is about 89%.

20 Next the hydroxy group of the alcohol is halogenated to yield a protected benzyl halide. For example, 3,5-dibenzyloxybenzyl alcohol is halogenated to give 3,5-dibenzyloxybenzyl halide. In one embodiment of the method, 3,5-dibenzyloxybenzyl alcohol is reacted with PBr_3 to give 3,5-dibenzyloxybenzyl bromide. The bromination step is about 90% efficient.

25 The protected benzyl halide is then phosphonated to give the produce the protected benzyl phosphonate described above. In one embodiment, 3,5-

dibenzoyloxybenzyl bromide is reacted with triisopropyl phosphite to produce isopropyl 3,5-dibenzoyloxybenzyl phosphonate in about a 94% yield.

Another method of synthesizing resveratrol uses a new, non-classical route involving palladium catalysis. The coupling step of this reaction is illustrated by the following formula:



wherein R¹ and R² are protecting groups such as methyl, alkyl, and benzyl. The starting material is coupled with a protected 4-hydroxystyrene via a Heck to produce a protected (E)-4-acetoxy stilbene. The aceto group is then removed under basic conditions to produce a protected 4'-hydroxystilbene. Next, the 3 and 5 protecting groups are removed to yield resveratrol.

In a presently preferred embodiment of the invention, a 3,5-substituted benzoic acid chloride was reacted with acetoxy styrene using catalytic amounts of palladium acetate and trialkylamine to give stilbene products. According to one presently preferred embodiment of this method, a quantity of 3,5-dimethoxybenzoyl chloride is obtained and coupled with 4-acetoxystyrene to form (E)-4-acetoxy-3',5'-dimethoxystilbene. A Heck reaction using a palladium catalyst is used for the coupling step. A base is added to the (E)-4-acetoxy-3',5'-dimethoxystilbene to remove the 4-aceto group and form (E)-3,5-dimethoxy-4'-hydroxystilbene. The methyl groups can be removed by the addition of BBr₃ to yield resveratrol.

All patents, publications, and commercial materials cited herein are hereby incorporated by reference.

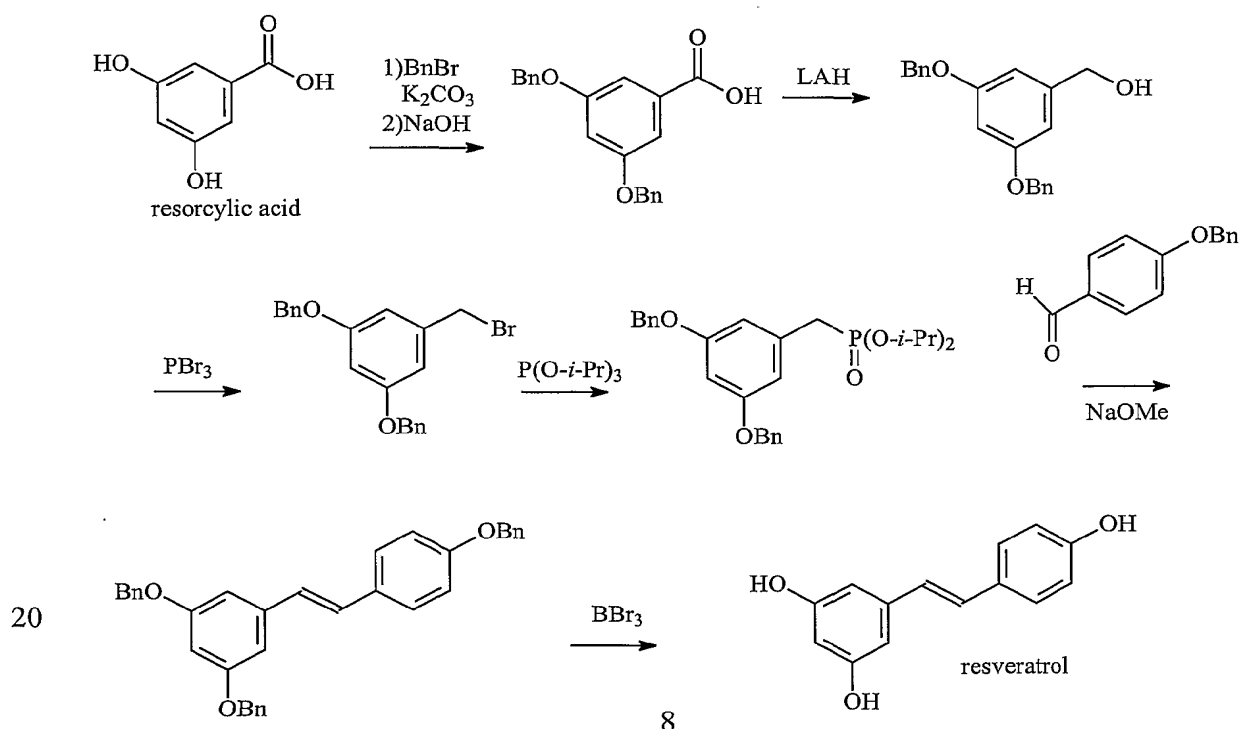
6. EXAMPLES

The following examples are given to illustrate various embodiments which have been made with the present invention. It is to be understood that the following examples

are not comprehensive or exhaustive of the many types of embodiments which can be prepared in accordance with the present invention.

Example 1 - Resveratrol Synthesis Via the Phosphonate Route

5 Resorcylic acid was reacted with benzyl bromide in acetone under basic conditions to give a protected benzyl ester. Treatment with KOH allowed for removal of the potassium benzoate from the benzyl alcohol by-product. The reaction mixture was acidified followed by LAH reduction to give benzyl alcohol in high overall yield. This procedure eliminates the need to chromatographically separate the benzyl alcohol. All
10 intermediates in the sequence were isolated by recrystallization. Conversion to the bromide was achieved using phosphorus tribromide. The Arbuzov reaction was then conducted using isopropyl phosphite to give the corresponding phosphonate in high yield. Coupling with 4-benzyloxybenzaldehyde at 1:1 stoichiometry with sodium methoxide gave the *E*-stilbene as a single isomer in good yield. The larger isopropyl phosphonate ensured complete *trans* alkene formation. All steps again to this point did not require
15 used of silica gel chromatography. Removal of the three benzyl ethers was performed by treatment with boron tribromide. Resveratrol was obtained identical in all respects to the naturally occurring material. The method of producing resveratrol is summarized in the following reaction.



This method of producing resveratrol can be readily scaled up for production of large amounts of resveratrol. Resorcylic acid, the starting material, is readily available and inexpensive. Moreover, the overall yield of the method from resorcylic acid to resveratrol is about 50%. The high yield and low cost of the reaction makes it ideal for large scale production.

Example 2 - 3,5-Dibenzyloxybenzoic Acid

A 500 mL round bottom flask was charged with 3,5-dihydroxybenzoic acid (7.03g, 45.4 mmol), 250 mL of acetone, potassium carbonate (12.6g, 90.8 mmol), benzyl bromide (16.2 mL, 136.0 mmol) and 18-crown-6 (0.490g, 1.36 mmol). The mixture was then heated to reflux for 48 h under a nitrogen atmosphere. The solution was then allowed to cool to ambient temperature where it was filtered and then concentrated in vacuo. The crude residue was then dissolved in 300 mL of EtOAc and the organic layer was subsequently washed with 250 mL of 1 M HCl and then 250 mL of brine. The organic phase was then dried over anhydrous MgSO_4 , filtered and concentrated. The residue was then taken up in 100 mL of 95% EtOH, 30 mL of H_2O and 20g of NaOH was added. The mixture was heated at reflux for 24 h and then cooled to ambient temperature and concentrated to dryness in vacuo. The crude material was then dissolved in H_2O and washed several times with Et_2O . The remaining aqueous layer was then acidified by the addition of HCl, at which point precipitation commenced. The resulting white crystals were then filtered and allowed to air dry to afford 3,5-dibenzyloxybenzoic acid in 70-80% yield. ^1H NMR (300 MHz, CDCl_3) δ 7.46-7.34 (m's, 12 H), 6.86 (t, $J = 2.40$ Hz, 1H), 5.10 (s, 4H); IR (cm^{-1}) 3371, 2916, 1695, 1597, 1423, 1379, 1347, 1303; HRMS calc'd (EI+) for $\text{C}_{21}\text{H}_{18}\text{O}_4$ 334.1205, found 334.1212.

Example 3 - 3,5-Dibenzyloxybenzyl Alcohol

A one-neck 100 mL round bottom flask equipped with a dropping funnel and reflux condenser under a nitrogen atmosphere was charged with LiAlH_4 (0.196g, 5.18 mmol), 5 mL of anhydrous Et_2O and cooled to 0 °C. The dropping funnel was charged with 3,5-Dibenzyloxybenzoic acid (1.73g, 5.18 mmol) and 60 mL of anhydrous Et_2O . The slurry of 3,5-Dibenzyloxybenzoic acid and Et_2O was allowed to drip into the stirring LAH solution over 2 h. Since the acid is not completely soluble in the Et_2O the flask was

allowed to warm to ambient temperature and then the mixture was heated at reflux for 7 h with continuous extraction of the remaining acid. After 7 h all the acid had been pulled into the flask and the solution was maintained at reflux for an additional 5 h. The solution was again cooled to 0 °C and then 10 mL of 4:1 Et₂O/MeOH solution was added dropwise to quench the excess LAH. The solution was warmed to ambient temperature and then diluted with 5 mL of H₂O. The solution was then washed with 50 mL of 1 M HCl. Separation of the layers was then followed by further extraction of the aqueous layer with Et₂O (4 x 50 mL). The combined organic layers were then dried over anhydrous MgSO₄, filtered and then concentrated to afford 3,5-dibenzyloxybenzyl alcohol, 1.36g (82%) as a white solid. ¹H NMR (300 MHz, CDCl₃) δ 7.45-7.33 (m's, 10H), 6.64 (d, *J* = 2.10 Hz, 2H), 6.56 (t, *J* = 2.10 Hz, 1H), 5.05 (s, 4H), 4.74 (s, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 160.4, 143.6, 137.1, 128.8, 128.2, 127.8, 106.0, 101.6, 70.3, 65.6; IR (cm⁻¹) 3319, 3032-2870, 1600, 1452, 1371, 1353, 1286; HRMS (EI+) calc'd for (M+) C₂₁H₂₀O₃ 320.1412, found 320.1425.

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Example 4 - 3,5-Dibenzyloxybenzyl Bromide

To a stirred solution of 3,5-Dibenzyloxybenzyl alcohol (1.18g, 3.69 mmol) in 20 mL of anhydrous Et₂O at ambient temperature under an atmosphere of nitrogen was added pyridine (0.009 mL, 0.112 mmol) and then PBr₃ (0.21 mL, 2.25 mmol) dropwise. The mixture was then warmed to reflux and maintained at that temperature for 3 h. The solution was then cooled to ambient temperature and poured over 25g of ice. After the ice had melted the layers were mixed and then separated. The aqueous layer was extracted further with Et₂O (3 x 25 mL). Then combined organic layers were then dried over anhydrous MgSO₄, filtered and concentrated to afford 3,5-dibenzyloxybenzyl bromide, 1.30g (92%), as a white solid. ¹H NMR (300 MHz, CDCl₃) δ 7.45-7.34 (m's, 10H), 6.66 (d, *J* = 2.40 Hz, 2H), 6.57 (t, *J* = 2.40 Hz, 1H), 5.04 (s, 4H), 4.43 (s, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 160.3, 136.8, 128.9, 128.3, 127.8, 108.4, 102.4, 100.2, 70.4, 33.8; HRMS (EI+) calc'd for (M+) C₂₁H₁₉BrO₂ 382.0568, found 382.0562.

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Example 5 - Isopropyl 3,5-dibenzyloxybenzyl Phosphonate

A 10 mL round bottom flask equipped with a distillation head was charged with 3,5-dibenzyloxybenzyl bromide (4.00g, 12.2 mmol) and 5 mL of triisopropyl phosphite. The

mixture was heated to 140-150 °C under nitrogen for 6 h. During this time, the evolved 2-bromopropane was collected. The solution was then cooled to ambient temperature and the excess triisopropyl phosphite was removed via vacuum distillation to afford isopropyl 3,5-dibenzyloxybenzyl phosphonate, 9.26g (94%), as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 7.46-7.34 (m's, 10H), 6.63 (bs, 2H), 6.55 (bs, 1H), 5.06 (s, 4H), 4.70-3.94 (m, 2H), 3.09 (d, *J* = 21.9 Hz, 2H), 1.32 (d, *J* = 6.30 Hz, 6H), 1.21 (d, *J* = 6.00 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 160.1, 160.0, 137.2, 134.2, 134.1, 128.8, 128.2, 127.8, 109.4, 109.3, 101.2, 101.1, 70.9, 70.8, 70.2, 36.3, 34.4, 24.4, 24.3, 24.2, 24.1; HRMS (EI+) calc'd for (M+) C₂₇H₃₃O₅P 468.2066, found 468.2074.

Example 6 - (E)-3,5,4'-Tribenzyloxystilbene

A 100 mL round bottom flask was charged with NaOMe (1.00g, 18.5 mmol), 20 mL of dry DMF and isopropyl 3,5-dibenzyloxybenzyl phosphonate (7.50g, 16.0 mmol). The mixture was then cooled to 0 °C under a nitrogen atmosphere and 4-benzyloxybenzaldehyde (4.00g, 18.8 mmol). The mixture was then allowed warm to ambient temperature and stand for 1 h. The mixture was then heated to 100 °C for 1 h and then allowed to stand at ambient temperature for 12 h. A water/ methanol (2:1, 30 mL) solution was then added and the precipitate was filtered, washed with hexanes and then recrystallized from MeOH to afford (E)-3,5,4'-tribenzyloxystilbene, 6.39g (80%) as a white solid. ¹H NMR (300 MHz, CDCl₃) δ 7.49-7.34 (m's, 17H), 7.06 (d, *J* = 16.4 Hz, 1H), 7.00 (d, *J* = 8.79 Hz, 2H), 6.92 (d, *J* = 16.1 Hz, 1H), 6.79 (d, *J* = 2.19 Hz, 2H), 6.57 (t, *J* = 2.19 Hz, 1H), 5.12 (s, 2H), 5.10 (s, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 160.4, 158.9, 140.0, 137.2, 130.4, 129.1, 128.9, 128.3, 128.1, 127.8, 127.8, 126.8, 115.3, 105.8, 101.4, 70.4, 70.3; HRMS (EI+) calc'd for (M+) C₃₅H₃₀O₃ 498.2195, found 498.2204.

Example 7 - (E)-3,5,4'-Trihydroxystilbene, Resveratrol

A 50 mL round bottom flask was charged with 3,5,4'-tribenzyloxystilbene (1.50g, 3.06 mmol) and 10 mL of anhydrous CH₂Cl₂. The resulting solution was then cooled to -60 °C under a nitrogen atmosphere. To the cooled solution was added BBr₃ (0.90 mL, 9.12 mmol) dropwise. The mixture was then allowed to warm gradually to ambient temperature and then allowed to stand at that temperature for 2 h. Then 10 mL of saturated NaHCO₃ solution was added to quench the reaction along with 15 mL of water.

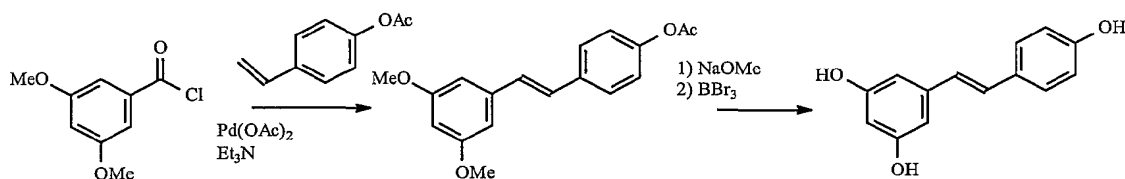
The solution was then diluted with 20 mL of EtOAc and the layers were subsequently mixed and separated. The aqueous layer was further extracted with EtOAc (3 x 20 mL). The combined organic layers were then dried with anhydrous MgSO_4 , filtered and then concentrated. Recrystallization followed by filtration afforded (E)-3,5,4'-

- 5 Trihydroxystilbene, (70-80%), as a tan solid. ^1H NMR (300 MHz, d_6 DMSO) δ 9.56 (bs, 1H), 9.21 (bs, 2H), 7.40 (d, $J = 8.70$ Hz, 2H), 6.94 (d, $J = 16.5$ Hz, 1H), 6.82 (d, $J = 16.5$ Hz, 1H), 6.76 (d, $J = 8.40$ Hz, 2H), 6.40 (d, $J = 2.10$ Hz, 2H), 6.13 (t, $J = 2.10$ Hz, 1H); ^{13}C NMR (75 MHz, d_6 DMSO) δ 158.5, 157.2, 139.3, 128.1, 127.9, 125.7, 115.5, 104.3, 101.8, 99.6.

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Example 8 - Reveratrol Synthesis Via the Decarbonylative Palladium Route

- An alternative method of producing resveratrol uses a newer, non-classical route involving palladium catalysis. 3,5-substituted benzoic acid chlorides were reacted with acetoxystyrene using catalytic amounts of palladium acetate and trialkylamine to give stilbene products. These conditions for the decarbonylative aromatic-olefin coupling reaction, a variation of the aryl halide-olefin Heck reaction with loss of carbon monoxide (CO), worked very well with unsubstituted acid chlorides giving yields of 80%. This method of producing resveratrol is summarized in the following reaction:



Example 9 - (E)-4-Acetoxy-3',5'-dimethoxystilbene

- 20 A flame dried 5 mL round bottom flask under a nitrogen atmosphere was charged with 3,5-dimethoxybenzoyl chloride (0.100g, 0.498 mmol), palladium (II) acetate (0.006g, 0.025 mmol) and 1.0 mL of dry *p*-xylene. The mixture was then stirred while 4-acetoxystyrene (0.095 mL, 0.622 mmol) was added via syringe. The mixture was then warmed to 120-130 °C and allowed to stir for 18 h. The dark mixture was then cooled to ambient temperature and filtered over a silica gel plug eluting with 50% EtOAc/hexanes. 25 The solution was then concentrated and the crude residue was purified via radial chromatography using 10% EtOAc/hexanes to afford (E)-4-acetoxy-3',5'-

dimethoxystilbene, 0.112g (75%), as white solid. ¹H NMR (300 MHz, CDCl₃) δ 7.52 (d, *J* = 8.70 Hz, 2H), 7.10 (d, *J* = 8.70 Hz, 2H), 7.08 (d, *J* = 15.9 Hz, 1H), 6.99 (d, *J* = 16.2 Hz, 1H), 6.68 (d, *J* = 2.40 Hz, 2H), 6.42 (t, *J* = 2.40 Hz, 1H), 3.84 (s, 6H), 2.32 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 169.6, 161.2, 150.3, 139.3, 135.1, 129.1, 128.3, 127.7, 122.0, 104.4, 100.2, 55.5, 21.3.

Example 10 - (E)-3,5-Dimethoxy-4'-hydroxystilbene

To a stirred solution of 4-Acetoxy-3',5'-dimethoxystilbene (0.380g, 1.28 mmol) in 5 mL THF, 2 mL H₂O, and 5 mL MeOH was added K₂CO₃ (0.530g, 3.82 mmol). The resulting yellow solution was allowed to stir at ambient temperature for 3 h. The solution was then carefully diluted with 20 mL 1 M HCl and 20 mL of EtOAc. The aqueous phase was extracted further with EtOAc (3 x 20 mL). The combined organic layers were then dried over anhydrous MgSO₄ concentrated to afford (E)-3,5-dimethoxy-4'-hydroxystilbene, 0.303g (93%), as a white solid. ¹H NMR (300 MHz, CDCl₃) δ 7.35 (d, *J* = 9.0 Hz, 2H), 7.00 (d, *J* = 16.2 Hz, 1H), 6.85 (d, *J* = 15.9 Hz, 1H), 6.82 (d, *J* = 8.70 Hz, 1H), 6.64 (d, *J* = 2.10 Hz, 2H), 6.37 (t, *J* = 2.10 Hz, 1H), 3.78 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 160.9, 155.9, 139.9, 129.7, 128.9, 128.1, 126.3, 115.8, 104.5, 99.7, 55.4.

Example 11 - (E)-3,5,4'-Trihydroxystilbene, Resveratrol

To a stirred solution of 3,5-Dimethoxy-4'-hydroxystilbene (0.415g, 1.62 mmol) in 40 mL of dry CH₂Cl₂ at -78 °C under a nitrogen atmosphere was added BBr₃ (0.74 mL, 7.82 mmol) dropwise. The solution was allowed to stir for 5 h while gradually warming to ambient temperature at which time the brown solution was quenched with a 10% KOH solution and allowed to stir for 0.5 h. The mixture was then acidified with 1 M HCl and extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were then dried over anhydrous MgSO₄ and filtered over a silica gel plug eluting with EtOAc. The material was concentrated and then purified via radial chromatography (20-50% EtOAc/hexanes) to afford (E)-3,5,4'-trihydroxystilbene (resveratrol), 0.211g (57%), as a tan solid. ¹H NMR (300 MHz, d₆ DMSO) δ 9.56 (bs, 1H), 9.21 (bs, 2H), 7.40 (d, *J* = 8.70 Hz, 2H), 6.94 (d, *J* = 16.5 Hz, 1H), 6.82 (d, *J* = 16.5 Hz, 1H), 6.76 (d, *J* = 8.40 Hz, 2H), 6.40 (d, *J* = 2.10 Hz, 2H), 6.13 (t, *J* = 2.10 Hz, 1H); ¹³C NMR (75 MHz, d₆ DMSO) δ 158.5, 157.2, 139.3, 128.1, 127.9, 125.7, 115.5, 104.3, 101.8, 99.6.

Summary

In summary, the present invention relates to novel methods of producing resveratrol, a naturally occurring compound that has shown potential in the treatment of cancer and other diseases. According to one aspect of the invention resveratrol can be made starting with resorcylic acid through a number of steps. The coupling of the modified resorcylic acid via a Horner-Emmons reaction yields a product that can be converted to resveratrol by removing protecting groups. In another embodiment of the invention, reaction products are coupled via a modified Heck reaction to form a protected 4'-hydroxystilbene that can also be converted to resveratrol by removing the protecting groups.

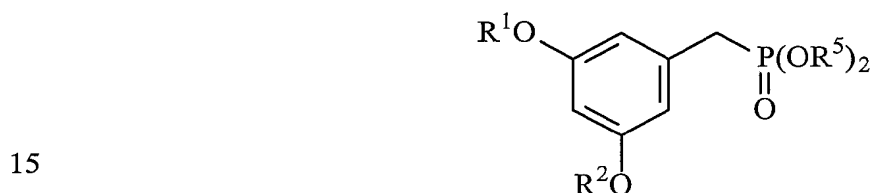
The invention may be embodied in other specific forms without departing from its essential characteristics. The described embodiments are to be considered in all respects only as illustrative and not restrictive. The scope of the invention is, therefore, indicated by the appended claims rather than by the foregoing description. All changes that come within the meaning and range of equivalency of the claims are to be embraced within their scope.

CLAIMS:

1. A method of making resveratrol comprising:
obtaining a first compound of the formula



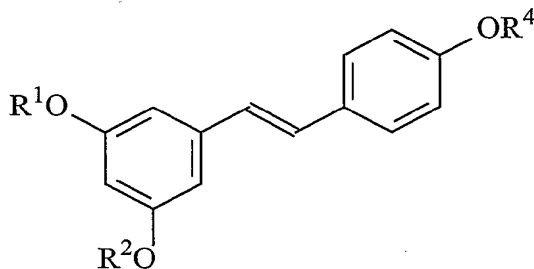
- wherein R¹ and R² are protecting groups and R³ is a halide; and
10 converting the first compound to a second compound of the formula



- to form a phosphonate, wherein R⁵ is an alkyl group; and
converting the second compound to resveratrol.

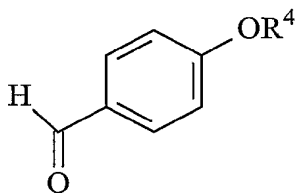
- 20
2. The method of claim 1, wherein the protecting groups are selected from the group consisting of a benzyl group, a methyl group, an alkyl group, and a silyl ester.
3. The method of claim 2, wherein R¹ and R² are identical.
- 25
4. The method of claim 1, wherein the first compound is converted to the second compound by reacting the first compound with an alkyl phosphite.

5. The method of claim 1, further comprising converting the second compound to a third compound of the formula



wherein R⁴ is a protecting group.

6. The method of claim 5, wherein the second compound is converted to the third compound by reacting the second compound with a fourth compound of the formula
- 15

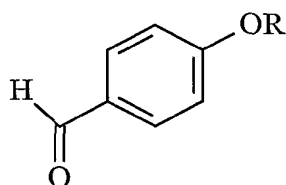


7. The method of claim 5, wherein R⁴ is selected from the group consisting of a methyl group, a benzyl group, and an alkyl group.
8. The method of claim 5, where in R¹, R², and R⁴ are identical.
- 25
9. The method of claim 5, further comprising removing the protecting groups to form resveratrol.

10. A method of synthesizing resveratrol comprising
obtaining 3,5-dihydroxybenzoic acid;
benzylating the 3 and 5 hydroxygroups to form 3,5-dibenzyloxybenzoic acid;
reducing the carboxylic group to form 3,5-dibenzyloxybenzyl alcohol;
5 brominating the reduced carboxylic group to form 3,5-dibenzyloxybenzyl
bromide;
reacting the 3,5-dibenzyloxybenzyl bromide with triisopropyl phosphite to form
isopropyl 3,5-dibenzyloxybenzyl phosphonate;
coupling the isopropyl 3,5-dibenzyloxybenzyl phosphonate with 4-
10 benzyloxybenzaldehyde to form (E)-3,5,4'-tribenzyloxystilbene; and
removing the benzyl groups to form resveratrol.

11. A method of synthesizing resveratrol comprising:
adding a protecting group to the 3 and 5 hydroxy groups of resorcylic acid;
15 reducing the carboxylic group of the protected resorcylic acid;
halogenating the reduced carboxylic group;
reacting the halogenated, reduced carboxylic group with an alkyl phosphite to
produce a phosphonate;
coupling the phosphonate with a compound of the formula

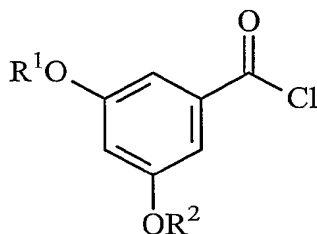
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- 25 via a Horner-Emmons reaction, wherein R is a protecting group; and
removing the protecting groups and the 4'-benzyl group to form resveratrol.

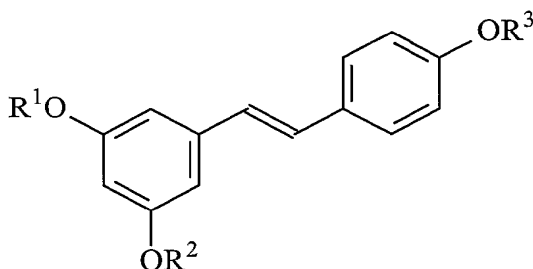
12. The method of claim 11, wherein the protecting groups are selected from the
group consisting of methyl, benzyl, and alkyl.
30
13. The method of claim 11, wherein each of the protecting groups are identical.

14. A method of synthesizing resveratrol, the method comprising:
obtaining a first compound of the formula



wherein R1 and R2 are protecting groups;

- 10 converting the first compound to a second compound of the formula



wherein R¹, R², and R³ are protecting groups; and
converting the second compound to resveratrol.

20

15. The method of claim 14, wherein the first compound is converted to the second compound by reacting the first compound with 4-acetoxystyrene.
16. The method of claim 14, further comprising removing the protecting groups.
- 25 17. The method of claim 14, wherein the protecting groups are selected from the group consisting of benzyl, methyl, silyl, and alkyl.
18. The method of claim 14, wherein the protecting groups are identical.

30

19. A method of synthesizing resveratrol comprising:
obtaining 3,5-dimethoxybenzoyl chloride; and
coupling the 3,5-dimethoxybenzoyl chloride with 4-acetoxystyrene to form (E)-4-acetoxy-3',5'-dimethoxystilbene.
- 5
20. The method of claim 19, further comprising removing the 4-aceto group of the (E)-4-acetoxy-3',5'-dimethoxystilbene to form (E)-3,5-dimethoxy-4'-hydroxystilbene.
- 10 21. The method of claim 20, further comprising removing the methyl groups of (E)-3,5-dimethoxy-4'-hydroxystilbene to form resveratrol.
22. A method of synthesizing resveratrol comprising:
obtaining 3,5-dimethoxybenzoyl chloride;
15 coupling the 3,5-dimethoxybenzoyl chloride with 4-acetoxystyrene to form (E)-4-acetoxy-3',5'-dimethoxystilbene;
removing the 4-aceto group of the (E)-4-acetoxy-3',5'-dimethoxystilbene to form (E)-3,5-dimethoxy-4'-hydroxystilbene; and
removing the methyl groups of (E)-3,5-dimethoxy-4'-hydroxystilbene to form
20 resveratrol.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US01/05167

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07C 39/12

- US CL : 568/729

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 568/729

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data-base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,335,055 A (BLASER et al) 15 June 1982, see entire document.	19-22
X	US 5,430,062 A (CUSHMAN et al) 04 July 1995, see column 10, lines 10-20 and top portion of column 49.	1-18
X,P	US 6,048,903 A (TOPPO) 11 April 2000, see columns 2 and 3.	1-18
X	GB 891,178 A (FARBWERKE HOECHST AKTIENGESELLSCHAFT) 14 March 1962, see entire document.	1-18
X	MEIER, H., Extension of the Squaraine Chromophore in Symmetrical Bis(stilbenyl)squaraines, J. Org. Chem., 1997, Vol. 62, pages 4821-4826.	1-18
X	ALONSO, E., Simple Synthesis of 5-Substituted Resorcinols, J. Org. Chem., 1997, Vol. 62, pages 417-421	1-18



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	
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"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

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27 April 2001 (27.04.2001)

Date of mailing of the international search report

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